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⑤4 1，2－ジヒドロ－3H－ピロロ〔3，2－e〕インドール誘導体の製法

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明細書

1　発明の名称

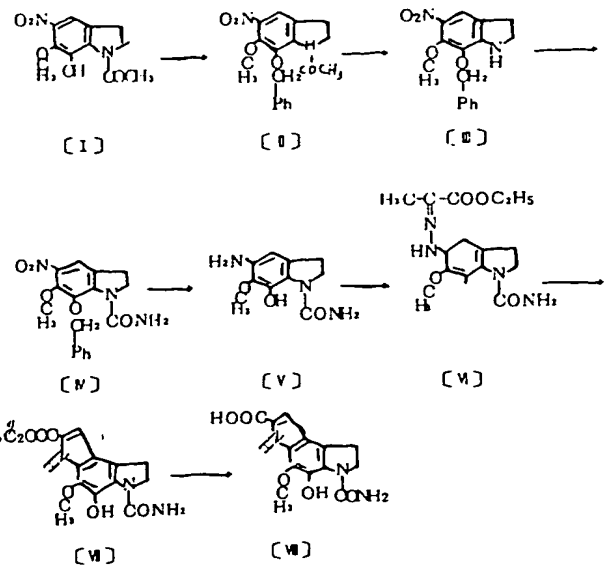
1，2－ジヒドロ－3H－ピロロ〔3，2－e〕インドール誘導体の製法

2　特許請求の範囲

1－アセチル－2，3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール－7－オールの水酸基をベンジル化し1－アセチル－7－ベンジロキシ－2，3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドールとし，次に脱アセチル化反応により7－ベンジロキシ－2，3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドールとする。ついでイソシアン酸を反応させ7－ベンジロキシ－2，3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール－1－カルボキシアミドとし還元的脱ベンジル化反応によつて5－アミノ－2，3－ジヒドロ－7－ヒドロキシ－6－メトキシ－1H－インドール－1－カルボキシアミドとする。次にジアゾ化しエチル－2－アセチルプロピオナートと反応させて2，3－ジヒドロ－5－〔N'－(1－エトキシカルボニルエチリデン)ヒドラジノ〕－7－ヒドロキシ－6－メトキシ－1H－インドール－1－カルボキシアミドとし環化によつてエチル－3－カルバモイル－1，2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3，2－e〕インドール－7－カルボキシレートとする。次にこれのアルカリ加水分解による3－カルバモイル－1，2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3，2－e〕インドール－7－カルボン酸の製造法。

3　発明の詳細な説明

本発明は酵素阻害剤として有用な公知化合物3－カルバモイル－1，2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－〔3，2－e〕インドール－7－カルボン酸の新規な製造法に関するものである。本発明の方法における反応は次式で示される。



〔I〕　〔II〕　〔III〕

〔IV〕　〔V〕　〔VI〕

〔VII〕　〔VIII〕

すなわち本発明の方法においては，上記反応式中における化合物〔I〕なる新規化合物の7位の水酸基を保護して化合物〔II〕とし，アルカリ加水分解によつて化合物〔III〕とする。ついで化合物〔III〕の1位をカルバモイル化して化合物〔IV〕としたのち水

素添加によつて化合物〔V〕とする。化合物〔V〕をジアゾ化したのちエチル-2-アセチルプロピオナートと反応させて化合物〔VI〕とし，化合物〔VI〕の環化により1,2-ジヒドロ-3H-ピロロ〔3,2-e〕インドール誘導体である化合物〔VII〕とし，化合物〔VII〕の加水分解によつて目的化合物3-カルバモイル-1,2-ジヒドロ-4-ヒドロキシ-5-メトキシ-3H-ピロロ〔3,2-e〕インドール-7-カルボン酸〔VIII〕を製造する。

本発明の方法によつて得られる3-カルバモイル-1,2-ジヒドロ-4-ヒドロキシ-5-メトキシ-3H-ピロロ〔3,2-e〕インドール7-カルボン酸は微生物代謝産物として得られたことが知られている〔特開昭52-18893〕が，まだこれを全合成した例はない。

この化合物は動物体内に存在するアデノシン3;5'-サイクリックリン酸ホスホジエステラーゼ（以下 サイクリック AMP PDEと呼ぶ）を阻害して，アデノシン3;5'-サイクリックリン酸（以下サイクリック AMPと呼ぶ）の分解を防ぎ，そ

の細胞内のレベルを制御することが知られ，それによる各種の薬理的効果が期待される。例えば肝臓における糖代謝の改善，強心作用，平滑筋弛緩作用，気管支拡張作用，冠状動脈拡張作用，脂質代謝の改善，精神安定作用，体液分泌促進作用，ホルモン分泌促進作用等を有する可能性がある。

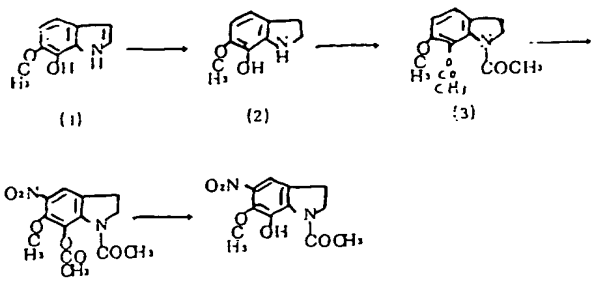
また高血圧ラットの血管中におけるサイクリック AMP含量の低い事が明らかとなり〔サイエンス，179巻 807ページ，1973年〕サイクリック AMP PDE阻害剤は抗高血圧作用や抗動脈硬化作用が期待されるし，アレルギーの発現にもサイクリック AMP が関与していることが発見され〔「バイオテク」3巻 No12，962ページ，1972年〕，サイクリック AMP PDE阻害剤が抗アレルギー，喘息防止作用等も予想される。

また サイクリック AMPの誘導体であるジブチリル アデノシン3'5'-サイクリック リン酸は培養動物細胞において，ガン細胞の増殖とガン化を抑制することが知られ〔蛋白質・核酸・酵素」18巻 No13，1195ページ，1973年〕この事はサ

イクリック AMP PDE阻害剤は抗ガン作用を有する可能性がある。更に具体的には サイクリック AMP PDEの阻害作用と精神薬との密接な関係も明らかにされている〔「サイエンス」176巻，428ページ，1972年〕。以上の如く本発明における目的化合物は医薬として広範な領域での利用が期待されている。

本発明における目的化合物は当初微生物代謝産物として単離されたものであるが収量も悪く，本発明者らは本化合物を化学的手法によつて得るべく検討を重ね本発明を完成したものである。

本発明で使用される原料化合物〔I〕は既述のように新規物質であるのでその調製法の一例を記載する。



(1)　(2)　(3)

(4)　〔I〕

すなわち，6－メトキシー1H－インドール－7－オール（公知物質）(1)を接触水素添加して2,3－ジヒドロ-6－メトキシー1H－インドール－7－オール(2)とし，ついでアセチル化して7－アセトキシー1－アセチル－2,3－ジヒドロ－6－メトキシー1Hインドールを得る。これをニトロ化して7－アセトキシー1－アセチル－2,3－ジヒドロ－6－メトキシー5－ニトロ－1H－インドール(4)とし，ついで部分加水分解によつて1－アセチル2,3－ジヒドロ－6－メトキシー5－ニトロ－1H－インドール－7－オール〔I〕を製造することが出来る。

さらに本発明の方法の実施を詳細に説明すれば，化合物〔I〕より化合物〔II〕の製造の目的は選択的水酸基の保護であり，後述のカルバモイル化反応における副反応を抑えることであり，その次の工程で1位のカルバモイル基や7位のメトキシ基を損なうことなく脱離しうる反応性に富む基であれば何れの保護基をも用いうる。かかる保護基としては置換アルキル基例えばベンジル基，置換ベンジル基等が適当である。例えば化合物〔I〕と塩化ベンジルとの反応では脱塩酸剤を用いメチルエチルケトン，THF，ジオキサン　DMF，DMSO，スルホラン等の不活性溶媒中70～150℃に加熱する事によつて目的を達する。

化合物〔II〕の脱アセチル化反応による化合物〔III〕の製造は通常の脱アセチル化反応の条件を用いればよく，有機溶媒例えばアルコール，ケトン，エーテル類中で化合物〔II〕を50～100℃でカ性アルカリと反応せしめればよい。

化合物〔III〕より化合物〔IV〕の製造は，2,3－ジヒドロ－1H－インドール誘導体の一位のカルバ

モイル化であり，一般には水－有機溶媒の混合液中で化合物〔III〕とイソシアン酸を反応させる。イソシアン酸は反応系において酸とイソシアン酸塩の反応で生成させて用いる。通常反応は水溶媒中においても行われるが，化合物〔IV〕の溶解度を高めるため有機溶媒との混合液中で行う。用いる有機溶媒としては本反応系に不活性な溶媒であればいずれでもよく，通常は酢酸，プロピオン酸等の有機酸，THF，ジオキサン等またアセトン，メチルエチルケトン等も用いうる。有機酸を用いる場合はイソシアン酸発生原料としての酸を必要としない。本発明で用いられる酸は塩酸，硫酸，有機酸であり，イソシアン酸塩としてはイソシアン酸カリウム，イソシアン酸ナトリウムを用いる。イソシアン酸塩は化合物〔III〕に対して1～10倍モルを用い，反応温度20～120℃，好ましくは80～100℃で1～2時間加熱する。

化合物〔IV〕より化合物〔V〕の製造は5位のニトロ基の還元と7位の保護基の脱離によるもので保護基がベンジル基の場合パラジウム－カーボンを

用い，室温～50℃で接触水素添加することによつて目的を達する。

化合物〔V〕より化合物〔VI〕の製造はピロール環合成に必要な側鎖の合成であり，すなわち化合物〔V〕をジアゾ化し，しかるのちにエチル－2－アセチルプロピオナートと反応せしめ1－エトキシカルボニルエチリデンヒドラジノ基を有する化合物〔VI〕とする。常法によつて得た化合物〔V〕のジアゾ化物とエチル－2－アセチルプロピオナートとの反応は，エチル－2－アセチルプロピオナートのアルカリ性溶液に前記ジアゾ化液を注入することによつて行われる。化合物〔V〕に対しエチル－2－アセチルプロピオナート1.0～1.2倍モルを用い，水と相溶性溶媒中でジアゾ化に用いた酸とほぼ等モルの苛性アルカリと低温，例えば－10～5℃で混合し，これに前記ジアゾ化液を－10～5℃で注入する。注入後さらに同温度で0.5～2時間反応させる。有利に用いられる有機溶媒としてはメタノール，エタノール等のアルコール類，アセトン，メチルエチルケトン等のケトン類，ジオ

キサン，THF等のエーテル類がある。

化合物〔VI〕の側鎖に環化反応を施してのピロール環合成による化合物〔VII〕の製造は環化剤として塩酸，硫酸，ポリリン酸等の酸を用いて行う。塩酸又は硫酸を用いる場合はアルコール溶媒中で，ポリリン酸を用いる場合は無溶媒で反応を行わせる。反応は室温もしくは加温下で行わせ，60～80℃まで加熱する場合もある。反応終了までに0.5～2時間を要する。

化合物〔VII〕より化合物〔I〕の製造は通常のエステルの加水分解反応であるが，化合物〔VII〕及び目的物〔I〕はアルカリ性下では比較的不安定なため希薄なアルカリ性下で反応するのがよく0.05～0.1Nの苛性アルカリを用い，アルコール等の有機溶媒中室温～50℃で0.5～24時間かきまぜる。反応終了後酸析し析出した結晶をとり，必要により再結晶，シリカゲルクロマトグラフィー又は再沈法等によつて精製する。

以下に本発明の方法で用いられる出発原料の調製を示す参考例並びに本発明の方法の実施を示す

参考例2　7－アセトキシ－1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール(4)の製造

7－アセトキシ－1－アセチル－2,3－ジヒドロ－6－メトキシ－1H－インドール5.0gを無水酢酸50mlと混合し，濃硝酸（d 1.50）1.5mlを0～2℃で滴下後さらに同温度で1時間反応させた。反応物を氷水に注入し，析出した結晶を戸取，水洗および乾燥したのちメタノールより再結晶してmp 161－162℃を有する淡黄色プリズム晶の7－アセトキシ－1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール4.0gをえた。元素分析値（カツコ内は計算値）：C% 53.47（53.06），H% 4.67（4.80），N% 10.33（9.52）。

参考例3　1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール－7－オール〔I〕の製造

7－アセトキシ－1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドー

実施例を上げて本発明を説明する。

参考例1　7－アセトキシ－1－アセチル－2,3－ジヒドロ－6－メトキシ－1H－インドール(3)の製造

6－メトキシ－1H－インドール－7－オール10g，5%－白金－カーボン4.0gおよび酢酸100mlを200mlのオートクレーブに装入し，水素ガスで初圧30kg/cm²とし40～50℃で圧力低下が認められなくなるまで反応させた。冷却後反応液を戸過し，戸液を減圧濃縮してえた粗製2,3－ジヒドロ－6－メトキシ－1H－インドール－7－オール酢酸塩をピリジン30mlに溶解し無水酢酸30mlを加え，室温で30分，60℃で3時間かきまぜた。反応液を減圧濃縮し，残分に水を加えてて更に減圧濃縮し，残分を四塩化炭素より再結晶してmp 141～142℃を有する7－アセトキシ－1－アセチル2,3－ジヒドロ－6－メトキシ－1H－インドール9.9gをえた。

元素分析値（カツコ内は計算値）：C% 62.16（62.64）
H% 5.84（6.07）N% 5.78（5.62）

ル3.7gをエタノール130mlに加え，10℃で2N－苛性ソーダ37mlを加え30分反応させた。水で希釈したのち濃塩酸で酸性化し，析出した結晶を戸取，水洗および乾燥したのちメタノールより再結晶してmp 146℃を有する黄色プリズム晶の1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール－7－オール2.6gをえた。元素分析値（カツコ内は計算値）：C% 52.74（52.38），H% 4.71（4.80），N% 11.44（11.11）。

実施例1　1－アセチル－7－ベンジロキシ－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール〔II〕の製造

1－アセチル－2,3－ジヒドロ－6－メトキシ－5－ニトロ－1H－インドール－7－オール2.2g，塩化ベンジル2.3gおよび無水炭酸カリウム5.5gをジメチルホルムアミド20mlと混合し110～120℃で30分加熱した。冷却後，戸過し，戸液を減圧濃縮してえた残分に酢酸エチルを加え，水洗，無水硫酸ナトリウムで脱水したの

さらに0～2℃で1時間かきまぜた。析出した結晶を採取，水洗および乾燥したのちエタノールより再結晶してmp 194～195℃を有する淡黄色リン片状晶の2,3－ジヒドロ－5－〔N'－（1－エトキシカルボニルエチリデン）ヒドラジノ〕－7－ヒドロキシ－6－メトキシ－1H－インドール－1－カルボキシアミド3.3 gをえた。NMR δ (DMSO-d6)：1.28（3H, t），2.08（3H, S），3.06（2H, t），3.79（3H, S），3.90（2H, t），4.23（2H, q），6.75（1H, S），6.88（2H, bs），8.47（1H, S），13.10（1H, S）。元素分析値（カッコ内は計算値）：C% 53.77（53.59），H% 6.03（5.95），N% 16.92（16.66）。

実施例6　エチル3－カルバモイル－1,2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3,2－e〕インドール－7－カルボキシレート〔Ⅵ〕の製造

2,3－ジヒドロ－5－〔N'－（1－エトキシカルボニルエチリデン）ヒドラジノ〕－7－ヒドロ

キシ－6－メトキシ－1Hインドール－1－カルボキシアミド8 gをエタノール400 mlに懸濁し塩化ガスを1時間導入した。ついで氷水に注入し，クロロホルムで抽出し，水洗，無水硫酸ナトリウムで脱水したのち減圧濃縮し，残分をクロロホルム－メタノール（20：1）を用いシリカゲルクロマトグラフィー精製し，更にクロロホルム－メタノールより再結晶してmp 213～216℃を有する無色針状結晶のエチル3－カルバモイル－1,2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3,2－e〕インドール－7－カルボキシレート1.0 gをえた。NMR δ (DMSO-d6)：1.35（3H, t），3.20（2H, t），3.83（3H, S），4.03（2H, t），4.27（2H, q），6.90（2H, S），7.00（1H, d），11.47（1H, S），13.00（1H, S）。元素分析値（カッコ内は計算値）：C% 52.26（56.42），H% 5.40（5.37），N% 13.01（13.16）。

実施例7　3－カルバモイル－1,2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3,2－e〕インドール－7－カルボン酸〔Ⅶ〕の製造

エチル3－カルバモイル－1,2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3,2－e〕インドール－7－カルボキシレート100 mgを0.05N－カ性カリ水溶液300 mlに溶解し，一夜放置したのち希塩酸にて酸性とし，酢酸エチルで抽出し，無水硫酸ナトリウムで脱水したのち減圧濃縮し，残分をクロロホルム－メタノール（3：1）を用い薄層クロマトグラフィー精製してmp 235℃（分解）を有する3－カルバモイル－1,2－ジヒドロ－4－ヒドロキシ－5－メトキシ－3H－ピロロ〔3,2－e〕インドール－7－カルボン酸55 mgをえた。NMR δ (DMSO-d6)：3.19（2H, t），3.78（3H, S），4.01（2H, t）6.84（1H, S），6.90（1H, d），11.23（1H, b.s），12.81（1H, S）。元素分析値（カッコ内は計算値）：C　53.48（53.61），H% 4.65（4.50），N% 14.37（14.43）。

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(Translation)

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Filing Date: March 31, 1978
Inventor: K. NIUCHI et al.
Applicant: Mitsui Toatsu Chemicals Inc.

SPECIFICATION

1. Title of the Invention

Method for producing 1,2-dihydro-3H-pyrrolo[3,2-e] indole derivative

2. Claim

A method for producing 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylic acid, wherein a hydroxyl group of 1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole-7-ol is benzylated to produce 1-acetyl-7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole; then causing a deacetylation reaction to produce 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole; then isocyanic acid is reacted to produce 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole-1-carboxy amide; then causing reductive debenzylation reaction to produce 5-amino-2,3-dihydro-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide; next diazotization and reaction with ethyl-2-acetyl propionate are performed to produce 2,3-dihydro-5-[N'-(1-ethoxy carbonyl ethylidene)hydrazino]-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide; cyclization is performed to produce ethyl-3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylate; and next, alkaline hydrolysis is caused to produce 3-

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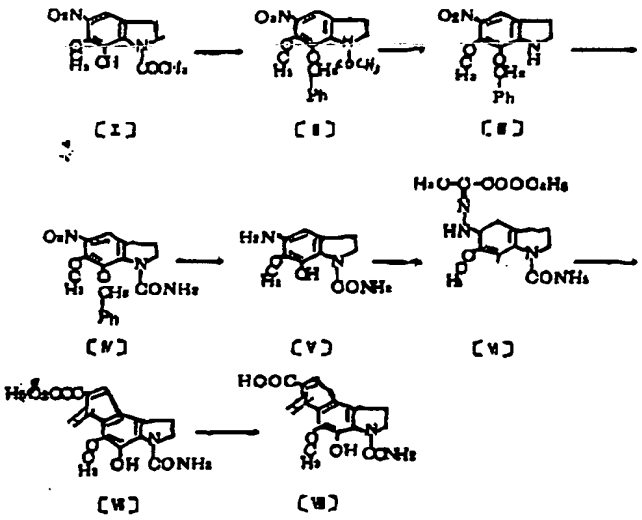
carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylic acid.

3. Detailed Description of the Invention

The present invention relates to a novel method for producing a known compound 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylic acid, which is useful as an enzyme inhibitor. The reaction by the method of the present invention is represented by the following scheme:



According to the method of the present invention, the hydroxyl group at position 7 of a novel compound, which is compound [I] in the above reaction scheme, is protected to produce compound [II], and then alkaline hydrolysis is caused to produce compound [III]. Then, position 1 of compound [III] is carbamoylated to produce compound [IV], and then hydrogen is added to produce compound [V]. The compound [V] is

diazotized and reacted with ethyl-2-acetyl propionate to produce compound [VI]. Then, the compound [VI] is cyclized to produce compound [VII], which is a 1,2-dihydro-3H-pyrrolo[3,2-e] indole derivative. The compound [VII] is hydrolyzed to produce the intended compound, 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo [3,2-e] indole 7-carboxylic acid [VIII].

The 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole 7-carboxylic acid obtained by the method of the present invention is known to have been obtained as a microorganism metabolite (Japanese Laid-Open Publication No. 52-18893), but there is no example reported so far of totally synthesizing this compound.

This compound is known as inhibiting adenocine 3',5'-cyclic phosphate phosphodiesterase (hereinafter, referred to as "cyclic AMP PDE") present in animal bodies so as to prevent decomposition of adenocine 3',5'-cyclic phosphate (hereinafter, referred to as "cyclic AMP") and thus to control the intracellular level thereof. The compound is expected to provide various pharmacological effects. The compound can possibly provide improvement of sugar metabolism in the liver, cardiotonic effects, smooth muscle relaxation effects, bronchodilation effects, coronary artery dilation effects, improvement of lipid metabolism, ataractic effects, bodily fluid secretion promoting effects, and hormone secretion promoting effects, and the like.

It has been found that high blood pressure rats have a low cyclic AMP content in their blood vessel ("Science", Vol. 179, page 807, 1973), and a cyclic AMP PDE inhibitor is expected to provide an antihypertensive effect and an

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anti-arterial sclerosis effect. It has been discovered that cyclic AMP is involved in the development of allergy ("Biotech", Vol. 3, No. 12, page 962, 1972). The cyclic AMP PDE inhibitor is expected to have anti-allergy effects, asthma prevention effects, and the like.

Dibutyl adenocine 3',5'-cyclic phosphate, which is a derivative of cyclic AMP, is known to suppress proliferation of cancerous cells and canceration in cultured animal cells ("Protein, Nucleic Acid, Enzyme", Vol. 18, No. 13, page 1195, 1973). This means that the cyclic AMP PDE inhibitor possibly has an anticancer effect. More specifically, the close relationship between the inhibition effect of cyclic AMP PDE and drugs for mental illness has been found ("Science", Vol. 176, page 428, 1972). As described above, the intended compound of the present invention is expected to be usable in a wide range of fields as a pharmaceutical drug.

The intended compound of the present invention was originally isolated as a microorganism metabolite, but the yield was low. The present inventors accumulated studies in order to obtain this compound by a chemical technique, and have completed the present invention.

The starting compound [I] used in the present invention is a novel substance as described above, and an exemplary method for preparing the starting compound [I] will be described.

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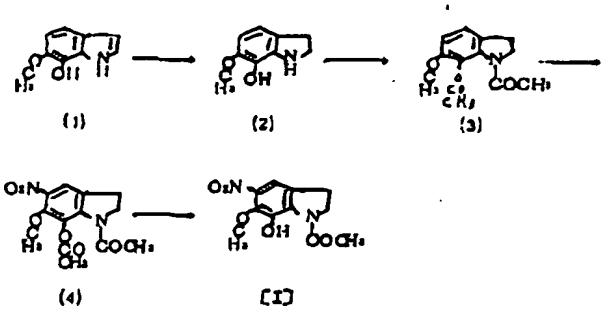

6-methoxy-1H-indole-7-ol (known substance) (1) is catalytically hydrogenated to produce 2,3-dihydro-6-methoxy-1H-indole-7-ol (2). This is acetylated to produce 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-1H indole. This is nitrated to produce 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole (4). Then, partial hydrolysis is performed to produce 1-acetyl 2,3-dihydro-6-methoxy-5-nitro-1H-indole-7-ol [I].

The practice of the method of the present invention will be described in more detail below. The purpose of producing compound [II] from compound [I] is to protect a free hydroxy group and thus to suppress the side reaction in the carbamoylation reaction described below. Any protecting group, which has sufficient reactivity to be removed in the subsequent step without spoiling the carbamoyl group at position 1 or the methoxy group at position 7, can be used. Appropriate protecting groups include substituted alkyl groups, for example, benzyl groups, substituted benzyl groups, and the like. For example, in the reaction of compound [I] and benzyl chloride, the objective is achieved by heating compound [I] and benzyl chloride with a de-chlorinating agent to 70 to 150°C in an inactive solvent such as methylethylketone, THF, dioxane, DMF,

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DMSO, sulfolane or the like.

Production of compound [III] by a de-acetylation reaction of compound [II] can be performed under usual de-acetylation reaction conditions, by reacting compound [II] with caustic alkali at 50 to 100°C in an organic solvent, for example, alcohol, ketone, or ethers.

Production of compound [IV] from compound [III] is carbamoylation of position 1 of a 2,3-dihydro-1H-indole derivative. In general, compound [III] and isocyanic acid are reacted in a water-organic solvent mixture solution. Isocyanic acid is generated by a reaction of an acid and an isocyanate in a reaction system. Usually, the reaction may be performed in an aqueous solvent, but is performed, here, in a mixture solution with an organic solvent in order to improve the solubility of compound [IV]. Any organic solvent which is inactive to the reaction system can be used. Usually, organic acids such as acetic acid, propionic acid and the like; THF; dioxane; acetone; methylethylketone and the like are used. When an organic acid is used, an acid as a material for producing isocyanic acid is not necessary. The acids used in the present invention are hydrochloric acid, sulfuric acid, and organic acids. As an isocyanate, potassium isocyanate or sodium isocyanate is used. The molar ratio of isocyanate is 1 to 10 times with respect to compound [III]. The reaction temperature is 20 to 120°C, preferably 80 to 100°C. Heating is performed for 1 to 2 hours.

Production of compound [V] from compound [IV] is realized by reduction of a nitro group at position 5 and removal of the protecting group at position 7. When the protecting group is a benzyl group, the objective is achieved by performing

catalytic hydrogenation using palladium-carbon at room temperature to 50°C.

Production of compound [VI] from compound [V] is synthesis of side chains necessary for synthesizing a pyrrole ring. This is performed by diazotizating compound [V], and then reacting with ethyl-2-acetyl propionate to produce compound [VI] having a 1-ethoxy carbonyl ethylidene hydrazino group. The reaction of the diazotized substance of compound [V] obtained by the usual method and ethyl-2-acetyl propionate is performed by injecting the diazotized solution into an alkaline solution of ethyl-2-acetyl propionate. Ethyl-2-acetyl propionate is used at a molar ratio 1.0 to 1.2 times with respect to compound [V], mixed in a solvent miscible with water with caustic alkali having substantially an equal molar ratio to the acid used for diazotization at low temperature (for example, -10 to 5°C). Then, the diazotized solution is poured into the resultant mixture at -10 to 5°C. After the injection, the reaction is continued for 0.5 to 2 hours at the same temperature. Advantageously usable organic solvents include alcohols such as methanol, ethanol and the like; ketones such as acetone, methylethylketone and the like; and ethers such as dioxane, THF and the like.

Production of compound [VII] by pyrrole ring synthesis by cyclization of the side chains of compound [VI] is performed using an acid such as hydrochloric acid, sulfuric acid, polyphosphoric acid or the like as a cyclization agent. When hydrochloric acid or sulfuric acid is used, the reaction is performed in an alcoholic solvent. When polyphosphoric acid is used, the reaction is performed with no solvent. The reaction is performed at room temperature or higher temperature. The temperature may be raised to 60 to 80°C. It requires 0.5

to 2 hours to complete the reaction.

Production of compound [VIII] from compound [VII] is a normal hydrolysis of ether. Compound [VII] and the intended compound [VIII] are relatively unstable under alkali, and are preferably reacted under dilute alkali. The compounds are stirred in an organic solvent such as, for example, alcohol, using 0.05 to 0.1 N caustic alkali, at room temperature to 50°C for 0.5 to 24 hours. After the reaction was completed, the precipitated crystals were removed. The resultant substance is purified by recrystallization, silica gel chromatography, or a re-precipitation method as necessary.

Hereinafter, the present invention will be described by way of reference examples representing preparation of the starting material used in the method of the present invention and examples of the present invention.

Reference example 1: Production of 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-1H-indole (3)

10 g of 6-methoxy-1H-indole-7-ol, 4.0 g of 5%-platinum-carbon, and 100 ml of acetic acid were placed in a 200 ml autoclave, and reacted with hydrogen gas at an initial pressure of 30 kg/cm^2 at 40 to 50°C, until the pressure reduction was not detected. After the resultant substance was cooled, the reaction solution was filtered. Crude 2,3-dihydro-6-methoxy-1H-indole-7-ol acetate, which was obtained by concentrating the filtrate under reduced pressure, was dissolved in 30 ml of pyridine; 30 ml of acetic anhydride was added; and the substances were stirred at room temperature for 30 minutes and then at 60°C for 3 hours. The reaction solution was concentrated under reduced pressure, and water was

added to the residue. The obtained substance was further concentrated under reduced pressure. The residue was recrystallized from carbon tetrachloride. Thus, 9.9 g of 7-acetoxy-1-acetyl 2,3-dihydro-6-methoxy-1H-indole having an mp of 141 to 142°C was obtained. Elemental analysis values (the values in brackets are calculated values): C% 62.16 (62.64); H% 5.84 (6.07); N% 5.78 (5.62).

Reference example 2: Production of 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H indole (4)

5.0 g of 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-1H-indole was mixed with 50 ml of acetic anhydride. 1.5 ml of concentrated nitric acid (d 1.50) was added dropwise at 0 to 2°C, and the reaction was continued for 1 hour at the same temperature. The reaction product was poured into iced water, and the precipitated crystals were filtered, washed with water, dried, and then recrystallized from methanol. Thus, 4.0 g of pale yellow prism-shaped crystals of 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole having an mp of 161 to 162°C was obtained. Elemental analysis values (the values in brackets are calculated values): C% 53.47 (53.06); H% 4.67 (4.80); N% 10.33 (9.52).

Reference example 3: Production of 1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole-7-ol [I]

3.7 g of 7-acetoxy-1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole was added to 130 ml of ethanol, and 37 ml of 2N-caustic soda was added at 10°C and reacted for 30 minutes. The resultant substance was diluted with water, and acidified with concentrated hydrochloric acid. The precipitated crystals were filtered, washed with water, dried, and then

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recrystallized from methanol. Thus, 2.6 g of yellow prism-shaped crystals of 1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole-7-ol having an mp of 146°C was obtained. Elemental analysis values (the values in brackets are calculated values): C% 52.74 (52.38); H% 4.71 (4.80); N% 11.44 (11.11).

Example 1: Production of 1-acetyl-7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole [II]

2.2 g of 1-acetyl-2,3-dihydro-6-methoxy-5-nitro-1H-indole-7-ol, 2.3 g of benzyl chloride, and 5.5 g of anhydrous potassium carbonate were mixed with 20 ml of dimethylformamide, and heated at 110 to 120°C for 30 minutes. The obtained substance was cooled and filtered, and the filtrate was concentrated under reduced pressure. Ethyl acetate was added to the resultant residue. The resultant residue was washed with water, de-watered with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was recrystallized from n-hexane-methylene chloride. Thus, 2.8 g of yellow prism-shaped crystals of 1-acetyl-7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole having an mp of 159°C was obtained. NMR δ ($CDCl_3$): 2.25 (3H, S), 2.92 (2H, t), 4.05 (2H, t), 4.10 (3H, S), 5.03 (2H, S), 7.38 (5H, S), 7.55 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 63.44 (63.15); H% 5.33 (5.30); N% 8.08 (8.18).

Example 2: Production of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole [III]

130 g of 1-acetyl-7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole was suspended in 250 ml of ethanol, 145 ml of

aqueous solution of 1N-caustic soda was added, and reacted at 70 to 80°C for 20 minutes. The resultant substance was cooled, then poured into water, extracted with ethyl acetate, washed with water, de-watered with anhydrous sodium sulfate, and concentrated under reduced pressure. Thus, 10.8 g of yellow needle-shaped crystals of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole having an mp of 93 to 94°C was obtained. NMR δ ($CDCl_3$): 3.02 (2H, t), 3.59 (2H, t), 3.98 (3H, S), 4.30 (1H, bs), 5.40 (2H, S), 7.44 (5H, S), 7.63 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 64.11 (63.99); H% 5.37 (5.38); N% 9.44 (9.33).

Example 3: Production of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole-1-carboxy amide [IV]

6.0 g of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole was dissolved in 90 ml of acetic acid, and 9 ml of water was added. The resultant substance was heated to 50 to 60°C, and an aqueous solution of 9.0 g of sodium isocyanate and 80 ml of water was dropped gradually. After the dropping was completed, the temperature was raised to 80 to 90°C, and reaction product was performed at this temperature for 1 hour. The reaction product was cooled and then poured into water. The precipitated crystals were filtered, washed with water and dried. Thus, 6.7 g of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole-1-carboxy amide having an mp of 184 to 186°C was obtained. NMR δ ($CDCl_3$): 3.02 (2H, t), 3.93 (3H, S), 4.08 (2H,t), 5.04 (2H, S), 6.78 (2H, S), 7.45 (5H, S), 7.61 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 60.19 (59.47); H% 4.98 (4.99); N% 12.29 (12.24).

Example 4: Production of 5-amino-2,3-dihydro-7-hydroxy-

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6-methoxy-1H-indole-1-carboxy amide [V]

6.1 g of 7-benzyloxy-2,3-dihydro-6-methoxy-5-nitro-1H-indole-1-carboxy amide, 2.0 g of 10%-palladium carbon, and 300 ml of ethanol were placed in an autoclave having a volume of 500 ml, and reacted with hydrogen gas at an initial pressure of 15 kg/cm^2 at room temperature, until the pressure reduction was not detected. After the reaction, the contents were filtered off, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from methanol. Thus, 3.5 g of white prism-shaped crystals of 5-amino-2,3-dihydro-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide having an mp of 196 to 197°C was obtained. NMR δ (DMSO-d_6): 2.90 (2H, t), 3.65 (3H, S), 3.81 (2H, t), 4.50 (2H, bs), 6.05 (1H, S), 6.67 (2H, S), 12.93 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 53,72 (53.80); H% 5.78 (5.87); N% 18.85 (18.83).

Example 5: Production of 2,3-dihydro-5-[N'-(1-ethoxy carbonyl ethylidene) hydrazino]-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide [VI]

2.5 g of 5-amino-2,3-dihydro-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide was added to 9.6 ml of a mixture of concentrated hydrochloric acid and 20 ml of water, and diazotized by adding a solution of 0.78 g of sodium nitrite and 8.8 ml of water at -5 to 0°C. Separately, 2.08 g of ethyl-2-acetyl propionate was dissolved in 25 ml of ethanol and cooled to -10°C or lower, and 12 ml of aqueous solution containing 4.5 g of caustic soda was added. To the resultant substance, the above-mentioned diazotized solution was poured at 2°C or lower, and stirred at 0 to 2°C for 1 hour. The precipitated crystals were filtered, washed with water, dried,

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and then recrystallized from methanol. Thus, 3.3 g of pale yellow flaky crystals of 2,3-dihydro-5-[N'-(1-ethoxy carbonyl ethylidene) hydrazino]-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide having an mp of 194 to 195°C was obtained. NMR δ (DMSO-d_6): 1.28 (3H, t), 2.08 (3H, S), 3.06 (2H, t), 3.79 (3H, S), 3.90 (2H, t), 4.23 (2H, q), 6.75 (1H, S), 6.88 (2H, bs), 8.47 (1H, S), 13.10 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 53.77 (53.59); H% 6.03 (5.95); N% 16.92 (16.66).

Example 6: Production of ethyl-3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylate [VII]

8 g of 2,3-dihydro-5-[N'-(1-ethoxy carbonyl ethylidene) hydrazino]-7-hydroxy-6-methoxy-1H-indole-1-carboxy amide was suspended in 400 ml of ethanol, and hydrogen chloride gas was introduced for 1 hour. Then, the resultant substance was poured into iced water, extracted with chloroform, washed with water, de-watered with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using chloroform-methanol (20:1), and recrystallized from chloroform-methanol. Thus, 1.0 g of colorless needle-like crystals of ethyl-3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylate having an mp of 213 to 216°C was obtained. NMR δ (DMSO-d_6): 1.35 (3H, t), 3.20 (2H, t), 3.83 (3H, S), 4.03 (2H, t), 4.27 (2H, q), 6.90 (2H, S), 7.00 (1H, d), 11.47 (1H, S), 13.00 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 52.26 (56.42); H% 5.40 (5.37); N% 13.01 (13.16).

Example 7: Production of 3-carbamoyl-1,2-dihydro-4-

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hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylic acid [VIII]

100 mg of ethyl-3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylate was dissolved in 300 ml of aqueous solution of 0.05 N-caustic alkali, left overnight, then acidified with diluted hydrochloric acid, extracted with ethyl acetate, de-watered with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by thin layer chromatography using chloroform-methanol (3:1). Thus, 55 mg of 3-carbamoyl-1,2-dihydro-4-hydroxy-5-methoxy-3H-pyrrolo[3,2-e] indole-7-carboxylic acid having an mp of 235°C (decomposed) was obtained. NMR δ (DMSO-d_6): 3.19 (2H, t), 3.78 (3H, S), 4.01 (2H, t), 6.84 (1H, S), 6.90 (1H, d), 11.23 (1H, bs), 12.81 (1H, S). Elemental analysis values (the values in brackets are calculated values): C% 53.48 (53.61); H% 4.65 (4.50); N% 14.37 (14.43).